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Ana Rita Gomes Teixeira Vaz

Efeito da corticoterapia antenatal na morbilidade e mortalidade de recém-nascidos pré-termo simples e gemelares / Effect of antenatal corticosteroids on morbidity and mortality in preterm singletons and twins

março, 2017

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Doutor Nuno Montenegro

E sob a Coorientação de:

Doutora Teresa Rodrigues

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UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO | MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Ana Rita Gomes Teixeira Vaz

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
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DESIGNAÇÃO DA ÁREA DO PROJECTO

Ginecologia e Obstetrícia

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Effect of antenatal corticosteroids on mortality and morbidity of preterm singletons and twins

ORIENTADOR

Professor Doutor Nuno Montenegro

COORIENTADOR (se aplicável)

Professora Doutora Teresa Rodrigues

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Faculdade de Medicina da Universidade do Porto, 1 / 3 / 2017

Assinatura conforme cartão de identificação: Ana Rita Gomes Teixeira Vaz

Effect of antenatal corticosteroids on morbidity and mortality in preterm singletons and twins.

Abstract

Purpose: Compare the effect of antenatal corticosteroids (ACS) on neonatal outcomes among singleton and twin pregnancies and the impact of completeness and timing of ministration.

Materials and Methods: Retrospective cohort study involving 951 preterm deliveries (25^{+0}-34^{+6}weeks), between 2006 and 2015. Neonatal outcomes were evaluated according to completeness of ACS ("Complete" n=441;"Rescue" n=38;"Incomplete" n=175;"No ACS" n=98) and timing of therapy related to delivery ("Before 7 days" n=260; "After 7 days" n=181).

Results: On Respiratory Distress Syndrome (RDS), odds ratio (OR) for twins was 0.172, 95% confidence interval (CI) 0.047;0.591 and for singletons 0.390 (95%CI 0.214;0.703) for complete or rescue courses, and 0.280 (95%CI 0.069;1.066) for twins and 0.906 (95%CI 0.482;1.698) for singletons for incomplete courses. About the need for mechanical ventilation (MV), twins had OR of 0.189 (95%CI 0.052;0.642) and singletons of 0.404 (95%CI 0.222;0.727) for complete or rescue courses and twins had OR=0.225 (95%CI 0.053;0.874) and singletons of 0.404 (95%CI 0.222;0.727) for incomplete courses. About timing, group "After 7 days" had OR=2.00 for RDS (95%CI 1.21;3.30) and 2.32 (95%CI 1.42;3.78) for MV.

Conclusion: ACS improves neonatal outcomes both in singleton and twins. Delivering seven days after a complete course decreased neonatal morbidity.

Key Words:

Antenatal corticosteroids; twins; preterm; morbidity.

Introduction

Preterm birth is the most costly complication of pregnancy and the leading cause of neonatal morbidity and mortality.[1,2] There are multiple strategies to minimize the risk and the impact of prematurity, such as ministration of antenatal corticosteroids (ACS), in association with tocolysis, neuroprotection with magnesium sulphate, and neonatal life-saving therapies.[3] These interventions improve neonatal survival after preterm birth.[4]

Since Liggins and Howie[5], numerous investigations have been conducted to ascertain the effect of ACS on prevention of neonatal morbidity and mortality in singleton pregnancies; nowadays, ACS are the cornerstone of prophylactic treatment in preterm birth, between 24^{+0} and 34^{+6} weeks of gestational age (GA), and its ministration is recommended by the National Institute of Health[2], the American College of Obstetricians and Gynecologists[6] and the Royal College of Obstetricians and Gynecologists[7]. When administered prior to preterm birth, ACS are not only effective in preventing respiratory distress syndrome (RDS) but also in reducing other complications of prematurity, such as intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), sepsis and necrotizing enterocolitis (NEC), and also neonatal mortality [3,4].Authors believe that, in order to achieve maximum effect, the ideal timing of delivery must occur between 24h and seven days after the last dose of therapy.[1,3,4,6,7]

Despite the significant amount of evidence supporting the impact of ACS in singleton pregnancies between 24 and 34^{+6} weeks of GA, there's a substantial lack of information regarding twin pregnancies.[8] The beneficial effect in singletons has justified ACS use in twin pregnancies, as the mechanism of action is likely to be the same, however the evidence is less robust.[1,4,7,9,10].

We aim to compare the effect of ACS in singleton and twin pregnancies in different neonatal outcomes. We have also tried to investigate the impact of therapeutic completeness (complete, incomplete or rescue) and timing (birth before or after seven days after the last ACS dose).

Materials and Methods

We performed a retrospective cohort study at *Centro Hospitalar de São João*, a tertiary level hospital in Portugal, with average 2500 deliveries per year, preterm (<37 weeks) rate of 10% and very preterm (<32 weeks) of 2%.

Maternal demographic and obstetric characteristics and neonatal outcomes of all singleton and twin pregnant women with preterm deliveries between 25 and 34^{+6} weeks from January 2006 to December 2015 *(n=951)* were evaluated. After the approval of the *Ethics Committee* of the hospital, medical records of both mothers and newborns were reviewed separately.

We excluded pregnancies with complications such as twin-to-twin transfusion syndrome (*n=19*), major fetal defects (*n=65*), triplet gestations (*n=5*) and women whose clinical records had important lack of information (n=25) or follow up losses (*n=46*).In order to increase internal validity, we eliminated pregnant women with less than 25 weeks of GA on admission (n=39) since none was exposed to ACS.

Maternal education, maternal age, body mass index (BMI), smoking habits, alcohol or drug abuse, parity, GA on admission and at the time of delivery, the mode of delivery, chorionicity in twins, *abruptio* placenta, fetal growth restriction (defined by Fenton`s growth charts [11]), fetal Doppler abnormalities, polihydramnios/oligohydramnios, preterm premature rupture of membranes (PPROM), diabetes, hypertensive, auto immune and thyroid diseases were evaluated.

We ascertained whether the mother received ACS, at which GA, the type of ACS, if the course completeness and the time interval (in days) between the first ministration and delivery, registering the same data for rescue courses. A course of ACS consisted on four 6*mg* doses of intramuscular dexamethasone at 12h intervals or two 12*mg* doses of intramuscular betamethasone at 24h interval, as the effect of these two types of ACS is apparently similar[2]. In our study, the ACS used before February 2014 was betamethasone, and since March 2014, dexamethasone.

For analysis, we divided this population in two major groups: "No ACS" group included pregnant women that were not submitted to antenatal corticosteroids *(n=98)* and the "ACS" group women exposed to this therapy *(n=654)*. "ACS" group was divided in three subgroups according to ACS completeness: "Complete" (women that had a complete course of ACS *(n=441)*), "Incomplete" (women submittted to less than the recommended dose (*n=175)*) and "Rescue" (women that had a complete or incomplete course of ACS, followed by another complete course two to three weeks after the first one (*n=38)*).

Our primary outcomes were Respiratory Distress Syndrome (RDS), diagnosed according to the criteria of the Update on the European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants (2013) [12] and the need for mechanic ventilation (MV). Secondary outcomes were neonatal death (defined as death in the first 28 days of life), admission to the NICU (Neonatal Intensive Care Unit), Apgar Index at the 1st and 5th minute of life, arterial pH value at birth, NEC (defined by the modified Bell staging criteria[13]), IVH (diagnosed and staged based on Papile classification [14]), sepsis, ROP (diagnosed and graded by the International Classification of Retinopathy of Prematurity revisited[15]) and need for phototherapy. We also performed a composite of neonatal morbidity that included RDS, NEC, ROP, IVH, sepsis and need for admission in the NICU.

The association between ACS and neonatal outcomes was evaluated for singletons and twins and adjusted for GA at delivery, weight of newborn and type of pregnancy (singleton *vs.* twins). For dichotomous neonatal outcomes, due the smaller sample size, the subgroups "Complete" and "Rescue" were grouped as one.

We also performed a subanalysis with the subgroup "Complete", subsequently divided in class "After 7 days" (if the birth happened more that seven days after the conclusion of the course) and "Before 7 days" (birth in the first seven days after completing the course).As we had only two participants that delivered prior to 24h after the last dose of ACS, we only separated the participants in 2 groups. Results for this analysis are presented in general due to loss of statistical power among twins and are adjusted for GA at delivery and weight of the newborn.

For continuous outcomes we used linear mixed effects analysis with random intercept per birth, when twins were included, and generalized least squares when twins were not included. Linear regression coefficients and the respective 95% confidence interval (95%CI) were used to estimate the association between the exposure and the respective outcome. A final model was estimated that included an interaction term between ACS group and being twin. For categorical outcomes we used unconditional logistic regression to estimate the odds ratios and the respective 95%CI. In twins, the data was aggregated and the outcome had considered when at least one of the twins had the outcome.

Results

In our study, 752 pregnancies were eligible from a total of 951 (79,1%); 199 were excluded by the aforementioned exclusion criteria. As so, 131 twins pregnancies and 621 singleton pregnancies were evaluated: 98 included in the "No ACS" group (76 singleton and 22 twins pregnancies), and 654 on the "ACS" group (545 singleton and 109 twins pregnancies). In this last group, 441 were in the "Complete" subgroup, 175 in the "Incomplete" and 38 in the "Rescue" subgroup. The pregnancies included in the "Complete" subgroup were then categorized according to timing as "After 7 days" (n=181) or "Before 7 days" (n=260).

The groups "No ACS" and "ACS" were similar regarding baseline maternal demographic and obstetric characteristics, except for chorioamnionitis, FGR, fetal Doppler abnormalities, mode of delivery and GA at admission (*table 1*).

Neonatal continuous outcomes according to ACS regimens are shown in *table 2*- in the composite of neonatal morbidity, twins had beta values (β) of -0.226 (95%CI -0.588;0.139) and singletons of -0.312 (95%CI -0.536; -0.088) if exposed to complete courses and β values of 0.044 (95%CI -0.364;0.451) in twins and 0.173 (95%CI 0.072;0.418) in singletons when exposed to incomplete courses.

For dichotomous neonatal outcomes, about need for admission in NICU, in singletons the odds ratio (OR) for complete or rescue courses was 0.887 (95%CI 0.427;1.740) and for incomplete courses 6.217(95%CI 2.212;20.265) and in twins OR for complete or rescue courses was 1.061(95%CI 0.286;3.528) and for incomplete courses 7.381(95%CI 1.046;149.349). Regarding RDS, in singletons OR for complete or rescue courses was 0.390 (95%CI 0.214;0.703) and for incomplete courses 0.906(95%CI 0.482;1.698) and in twins OR for complete or rescue courses was 0.172(95%CI 0.047;0.591) and for incomplete courses 0.280(95%CI 0.069;1.066); about the need for phototherapy, in singletons OR for complete or rescue courses was 1.261 (95%CI 0.865; 1.86) and for incomplete courses 1.515(95%CI 1.010;2.294) and in twins (OR for complete or rescue courses was 0.813(95%CI 0.270;2.287) and for incomplete courses 1.252(95%CI 0.367;4.180). Concerning MV need, in singletons OR for complete or rescue courses was 0.404(95%CI 0.222;0.727) and for incomplete courses 0.819(95%CI 0.435;1.535) and in twins OR for complete or rescue courses was 0.189(95%CI 0.052;0.642) and for incomplete courses 0.225 (95%CI 0.053;0.874). We couldn't find significant differences for the variables neonatal death, NEC, IVH, ROP and sepsis.

Neonatal outcomes according to timing are shown in *table 3*: in RDS, the OR for the group "After 7 days" was 2 (95%CI 1.21;3.30), and in almost all analyzed variables this

group was positively associated with adverse outcomes.

Discussion

Improving pregnancy outcomes is a major goal of healthcare today, and with ACS many premature lives have been saved. The success of this therapy is explained by the fact that synthetic glucocorticoids mimic the developmental maturational changes that normally occur in late gestation in response to rising fetal glucocorticoids.

Despite abundant evidence that use of ACS in singleton pregnant women who are in risk of PTL, between 24 and 34^{+6} weeks, has important benefits, data in twin pregnancies the data is limited [1,3,4,7,8-10,16-20].

Our main research question was to determine if clinical neonatal outcomes were equivalent when women received the same therapeutic scheme, independently of plurality.

We started to evaluate maternal characteristics *(table 1):* in 26 parameters, only in five (incidence of chorioamnionitis, fetal growth restriction (FGR), Fetal Doppler abnormalities, mode of delivery and mean GA at admission) there was significant differences between the "No ACS" and the "ACS" group. The higher rate of chorioamnionitis in the "No ACS" group may possibly be explained by less usage of ACS in these patients. FGR and fetal Doppler abnormalities were more common in the “ACS” group possibly because there's a more aggressive treatment in this higher risk groups. Regarding the mode of delivery, the majority of the vaginal preterm births occurred amongst women in the "No ACS" group (in fact, being already in labour was the main reason for not receiving ACS between our participants) with high rates of caesarean delivery in the "ACS" group. Furthermore, we analyzed the frequency of elective and urgent caesareans, and probably because these were the most severe cases of fetal compromise, results showed that the majority of urgent caesareans occurred in the "No ACS" group. Since the association between ACS and neonatal outcomes was not changed after inclusion of mode of delivery in the multivariable model, the final analysis wasn't adjusted for this characteristic.

We analyzed the impact of ACS completeness and timing of delivery. In general, and about the completeness, having a complete or rescue course was better than an incomplete course or no treatment, which may be attributed to inadequate dose or duration of exposure, as it was shown in other studies[21]. About the impact of different timings between the last ACS dose and delivery, the analysis wasn’t able to compare singletons with twins because of our sample size, but the absence of statistical interaction lead us to the presupposition that the effect is similar between this two groups. Delivery in the first seven days after conclusion

of this therapy was significantly associated with lower probability of neonatal death, RDS and need for MV, and despite no statistical significance, other outcomes were compatible, suggesting lower probabilities of developing NEC, need for phototherapy or admission to NICU, and also higher values of umbilical arterial pH, Apgar index at 1st and 5th minute of life and number of days at NICU. Though, the IVH was an exception: our results suggest that newborns delivered more than seven days after ministration had lower rates of this disease, a finding perhaps circumstantial but that can also be explained by the fact the higher GAs at admission are associated with lower prematurity associated complications. Our results in the timing sub analysis are also compatible with literature: Blickstein et al.[22] found that if the delivery occurred seven days past the ministration, there was no effect in the reduction of RDS, in comparison with delivering in the first seven days, both singleton and twins. Moreover, Gyamfi et al[10] agreed by demonstrating that concentrations of betamethasone in cord blood decreased over time, irrespective to plurality.

However, our main research question was to evaluated if results in twins were comparable to singletons. Although in singletons there's a generalized consensus of administration of ACS, twins are treated by extrapolation. In the set of continuous variables, participants were divided in the three subgroups aforesaid ("Complete", "Incomplete" and "Rescue"). In the composite of neonatal morbidity, Apgar indexes and number of days at NICU, there were no differences between singletons and twins, so we believe that the effect of complete courses was equally protective. About the NICU admission, RDS, need for phototherapy and MV, in both singleton and twins doing a rescue or complete course was better than doing an incomplete one, which was also better than no treatment at all. When evaluating the difference of impact of ACS completeness in twins versus singletons [23], we found that concerning admission in NICU, the association was 20% lower, so we believe that effect is similar in singletons and twins. In respect of RDS, as the association was 43% higher in singletons, we report that when twin pregnancies are submitted to complete regimens, they have less risk of developing this condition, in comparison with singletons. Also, about the need for MV and phototherapy, the difference was of 46% and 67%, respectively, with higher protection in twin pregnancies. So, our results suggest that despite ACS protection both in singletons and twins, on respect of respiratory outcomes, twins may possibly be more protected.

Authors suggest that ACS ministration doesn't reduce the incidence of RDS in preterm twins as it does in singletons, so that there's an interaction with plurality [1, 3,16-18] . Because the recommended dose of ACS is administered irrespective of maternal mass or fetal number, it has been hypothesized that the supposed suboptimal benefits of ACS

treatment in twin pregnancies may be attributable to greater degrees of maternal physiological changes in twin pregnancies, such as greater maternal blood volume expansion and different clearance of betamethasone[24].

However, this hypothesis was challenged by recent studies that demonstrated no difference between either the pharmacokinetics (clearance and volume of distribution) or the maternal serum or cord blood concentrations between singletons and twins[10,19]. Other studies report that the effect of ACS is present in twin pregnancies, so that the actual dosage and timing is effective [1,8,9,19,20]. Recently, Salim et al. demonstrated that serum betamethasone concentration is measurable with ELISA kit, paving the way for future investigations to determine the optimum concentration that would be clinically[25].

Our results are in this perspective too: apparently the number of fetus isn't a determinant of the effect of this therapy in the majority of our evaluated outcomes, so that giving this therapy to singleton or twin pregnant women seems to produce the same effects. We also highlight that, in the respiratory outcomes, when exposed to the same therapeutic scheme, twins were even more protected. However, there's still need to be sure which dosage of ACS is effective not only in singletons but mostly in twin pregnancies.

Our study had several strengths: the inclusion criteria were broad, and the analysis did not exclude fetal abnormalities compatible with life. In contrast to other studies examining neonatal outcomes, we included detailed antenatal and pregnancy characteristics. Though, the inherent weaknesses of a cohort study design should be recognized: the retrospective nature invites the possibility of sampling bias leading to differences in major adverse outcome measures. Also, the number of patients was not large enough to allow us to have statistically significant results in all of our outcomes, which is not unique to our study.

Although we think it would be important to differentiate between mono and dichorionic twin pregnancies, we did not have enough sample size to perform this analysis. Further observational studies in large cohorts of twins are warranted to increase the power to find differences in neonatal outcomes, as well as increase our confidence in the safety of using this dose and timing of ACS in twin pregnancies, but we highlight the possible ethical issues that may rise with the omission of therapy to the "control" group. A large, randomized, prospective trial would evaluate the difference of impact of the corticotherapy in singleton and twin pregnancy.

In conclusion, there were differences in the effect of ACS between singletons and twins in RDS, need for MV and phototherapy.

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Disclosure Statement

The authors report no conflicts of interest.

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Table 1: Maternal Demographic and Obstetric Charateristics.

	TOTAL	NO ACS (n (%))	ACS (n (%))	p value
Years of education				0.931
<12 years	276	34 (12.3)	242 (87.7)	
> 12 years	432	51 (11.8)	381 (88.2)	
Tobacco				0.867
Yes	50	7 (14.0)	43 (86.0)	
Alcohol				0.379
Yes	6	2 (33.3)	4 (66.7)	
Drugs				0.270
Yes	1	1 (100)	0 (0)	
Parity				0.927
Nulliparous	361	46 (12.7)	315 (87.3)	
Multiparous	393	52 (13.2)	341 (86.8)	
Conception				0.255
Not Spontaneous	75	6 (8.0)	69 (92.0)	
Spontaneous	665	89 (13.4)	576 (86.6)	
DM				0.788
Yes	87	10 (11.5)	77 (88.5)	
Hypertensive Disease				0.383
Yes	176	19 (10.8)	157 (89.2)	
Mode of Delivery				<0.001
Vaginal	37	11 (29.7)	26 (70.3)	
Urgent Cesariane	323	44 (13.6)	279 (86.4)	
Eletive Cesariane	123	7 (5.70	116(94.3)	
Polihydramnios/Oligohydramnios				0.102
Yes	115	9(7.8)	106(92.2)	
PPROM				0.346
Yes	253	28 (11.1)	225 (88.9)	
***Abruptio* Placenta**				0.093
Yes	39	9 (23.1)	30 (76.9)	
FGR				0.014
Yes	169	12(7.1)	157(92.9)	
DFA				0.005

Yes	113	5 (4.4)	108(95.6)	
Thyroid pathology				0.879
Yes	37	4 (10.8)	33 (89.2)	
Chorioamnionitis				0.036
Yes	6	3 (50.0)	3 (50.0)	
Auto-Immune Diseases				0.819
Yes	22	2 (9.1)	20 (90.9)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Maternal Age	31.03 (5.91)	31.60 (6.436)	30.94 (5.833)	0.931
Body Mass Index	26.57 (5.299)	27.57 (5.84)	26.438 (5.21)	0.115
GA at admission	32.17 (2.56)	33.10 (2.38)	32.03 (2.56)	<0.001

DFA: Doppler blood flow abnormalities; DM: Diabetes Mellitus; FGR: Fetal Growth Restriction; GA: Gestational Age

Table 2: Impact of different ACS regimens in neonatal outcomes represented by continuous variables

	TOTAL[1]	TWINS	SINGLETON	p interaction
	β (95% CI)	**β (95% CI)**	**β (95% CI)**	
Apgar 1				0.760
No ACS (Ref)	Ref	Ref	Ref	
Complete	0.833(0.430;1.23)	1.18 (0.544;1.81)	0.707 (0.210;1.20)	
Incomplete	0.289 (-0.160;0.737)	0.289 (-0.434;1.01)	0.269 (-0.280;0.819)	
Rescue	1.419(0.737;2.10)	1.81(0.739;2.886)	1.30(0.467;2.15)	
Apgar 5				0.428
No ACS(Ref)	Ref	Ref	Ref	
Complete	0.627 (0.292;0.960)	0.759 (0.272;1.246)	0.573 (0.150;0.996)	
Incomplete	0.385 (0.014;0.756)	0.041 (-0.512;0.595)	0.489 (0.022;0.955)	
Rescue	1.214(0.651;1.77)	1.21(0.385;2.03)	1.237(0.522;1.951)	
pH				0.657
No ACS(Ref)	Ref	Ref	Ref	
Complete	0.051(0.014;0.090)	0.0248 (-0.023;0.0734)	0.060(0.013;0.107)	
Incomplete	0.020 (-0.022;0.062)	-0.0245 (-0.077;0.0286)	0.034 (-0.079;0.085)	
Rescue	0.059(0.003;0.115)	0.0367(-0.036;0.101)	0.061(-0.008;0.130)	
Days at NICU				0.667
No ACS(Ref)	Ref	Ref	Ref	
Complete	-3.19 (-7.81;1.44)	-2.44 (-9.94;5.052)	-2.98 (-8.61;2.64)	
Incomplete	0.484 (-4.67;5.63)	-1.62 (-10.22;6.971)	1.47 (-4.74;7.69)	
Rescue	-0.916(-8.74;6.91)	6.99(-5.73;19.73)	-2.54 (-12.07;6.97)	
Composite				0.800
No ACS	Ref	Ref	Ref	
Complete	-0.301 (-0.492; -0.110)	-0.224 (-0.588; 0.139)	-0.312 (-0.536 ; -0.088)	
Incomplete	0.142 (-0.067; 0.352)	0.044 (-0.364 ; 0.451)	0.173 (-0.072 ; 0.418)	
Rescue	-0.297 (-0.596; 0.036)	-0.166 (-0.766;0.434)	-0.298 (-0.670;0.074)	

β: beta-value; 95%CI: 95% Confidence Interval NICU: Neonatal Intensive Care Unit; Apgar1: Apgar Index at 1st minute of life; Apgar5: Apgar index at the 5th minute of life; Composite: Included RDS, NEC, IVH, ROP, sepsis and need for admission in the NICU.

[1] Adjusted for type of pregnancy (singleton or twins), gestational age at delivery and weight of the newborn.

Table 3: Impact of different ACS timings in neonatal outcomes

	β (95% CI)
Apgar 1	
Before 7 days	Ref
After 7 days	-0.057 (-0.410;0.295)
Apgar 5	
Before 7 days	Ref
After 7 days	-0.042 (-0.351;0.266)
pH	
Before 7 days	Ref
After 7 days	-0.025 (-0.055;0.0055)
Days at NICU	
Before 7 days	Ref
After 7 days	0.826 (-3.332 ; 4.98)
	OR (95% CI)
NICU	
Before 7 days	Ref
After 7 days	1.093 (0.631 ; 1.894)
RDS	
Before 7 days	Ref
After 7 days	2.00 (1.21;3.30)
NEC	
Before 7 days	Ref
After 7 days	1.56 (0.56;4.34)
Photo	
Before 7 days	Ref
After 7 days	1.075 (0.68 ; 1.70)
IVH	
Before 7 days	Ref
After 7 days	0.673 (0.233;1.94)
Death	
Before 7 days	Ref
After 7 days	2.20 (1.016;4.77)
MV	
Before 7 days	Ref
After 7 days	2.32 (1.42;3.78)

β: beta-value; OR: Odds Ratio; 95%CI: 95% Confidence Interval; NICU: Neonatal Intensive Care Unit; Apgar1: Apgar Index at 1st minute of life; Apgar5: Apgar index at the 5th minute of life; RDS: Respiratory distress syndrome; NEC: Necrotizing enterocolitis; Photo: phototherapy; IVH: Intraventricular hemorrhage; MV: Mechanical ventilation. Adjusted for type of pregnancy (singleton or twins) and weight of the newborn.

ANEXO 1 - Regras da Revista Journal of Maternal, Fetal & Neonatal Medicine

The Journal of Maternal-Fetal & Neonatal Medicine publishes the following types of articles: The space available in the printed journal is restricted and authors should follow the below word limits, otherwise this may result in their submission being un-submitted or delayed.

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Short Reports: These should be of original laboratory or clinical contributions. The maximum length is 1500 words (excluding references), including headings and 100-word abstract, maximum of 1 figure and/or table, and up to 10 references.
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Please write clearly and concisely, stating your objectives clearly and defining your terms. Your arguments should be substantiated with well reasoned supporting evidence.
In writing your paper, you are encouraged to review articles in the area you are addressing which have been previously published in the Journal, and where you feel appropriate, to reference them. This will enhance context, coherence, and continuity for our readers.
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